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Evidence-based Series Special Report 4-7 EDUCATION AND INFORMATION 2011

Alternative and Complementary Therapy in the Prevention and Management of Gynecologic Cancers

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Practice Guideline Report 4-7 was reviewed and put in the Education and Information section in September 2011.The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).
The reviewed report consists of:

1. **Guideline Report Overview**
2. **Summary**
3. **Full Report Document Assessment and Review Tool**

and is available on the CCO Web site (http://www.cancercare.on.ca)
PEBC Gynecologic Cancer Disease Site Group page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/gynecologic_cancer/.

Release Date: June 25, 2012

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/
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EBS Special Report (Vancouver Style): Alternative and complementary therapy in the prevention and management of gynecologic cancers. . Toronto (ON): Cancer Care Ontario; 2012 Apr 3 [Education and Information 2011 Sep]. Program in Evidence-based Care Evidence-based Series Special Report No.: 4-7 Education and Information 2011.

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Evidence-based Series Special Report 4-7 EDUCATION AND INFORMATION 2011

Alternative and Complementary Therapy in the Prevention and Management of Gynecologic Cancers

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version October 2004	1985-2004	Full Report	Web publication	Not applicable (NA)
Reviewed Version April 2012	N/A	N/A	Updated Web publication	Guideline ARCHIVED

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Evidence-based Series Special Report 4-7 ARCHIVED 2011

Alternative and Complementary Therapy in the Prevention and Management of Gynecologic Cancers

Guideline Review Summary

Review Date: September 2011

The 2004 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2004. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Summary and Full Report in this version are the same as October 2004 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is completed with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore no update search was conducted. The 2004 guideline and its recommendations on Alternative and Complementary Therapy in the Prevention and Management of Gynecologic Cancers have been ARCHIVED.

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Evidence-based Series Special Report 4-7 ARCHIVED 2011

Alternative and Complementary Therapy in the Prevention and Management of Gynecologic Cancers

C. Briere, D. Dal Bello, M. Fung Kee Fung, A. Chambers, and members of the Gynecology Cancer Disease Site Group

Report Date: October 22, 2004

This special report is a systematic overview of the best evidence available on alternative and complementary therapy for women with gynecological cancers. This review has been written and opinions have been formed by the Gynecology Cancer Disease Site Group, which consists of gynecologists, oncologists, an oncology nurse, patient representatives, and methodologists.

SUMMARY

Questions

1. What complementary or alternative medicine therapies are available to women with gynecological cancers?
2. How safe are the complementary or alternative medicine therapies available to women with gynecological cancers?

Target Population

This special report applies to women seeking or using complementary or alternative medicine therapies to prevent or treat a gynecological cancer.

Opinions of the Gynecology Cancer Disease Site Group

The lack of sufficient high-quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer Disease Site Group offers the following opinions based on the evidence reviewed:

- From the evidence available from randomized controlled trials investigating complementary or alternative medicine therapies for the prevention or treatment of malignancies of all types, the Gynecology Cancer Disease Site Group feels that:
  - Women with gynecological malignancies should be discouraged from using high dosages of vitamin A for the purpose of delaying progression of the malignancy. Not only are high dosages of vitamin A highly toxic but also there is no evidence to support that high dosages of vitamin A are beneficial.
  - Women with gynecological malignancies may be encouraged to engage in physical activity (if possible) or relaxation therapy to improve physical and psychological function.
  - There is some evidence suggesting that high dosages of vitamin C are not beneficial; however, the evidence is not specific to women with gynecological cancers. High doses of vitamin C have anticoagulant effects, which could potentially increase the risk of bleeding in patients who are undergoing surgery or are thrombocytopenic.

- The Gynecology Cancer Disease Site Group is unable to support or refute the use of any other complementary or alternative medicine therapy based on the limited evidence.

- Practitioners and patients are encouraged to openly discuss and disclose the use of complementary or alternative medicine therapies. Disclosing the use of complementary or alternative medicine therapies will allow practitioners to provide assistance and guidance to the extent possible with respect to any potential harms or benefits known to be associated with the use of the therapies.

Methods

Entries to MEDLINE (1985 to April 2004), CANCERLIT (1985 to October 2002), AMED (Allied and Complementary Medicine) (1985 to March 2004) and Cochrane Library (2004, issue 1) databases and abstracts published in the proceedings of the annual meetings of American Society of Clinical Oncologists (1997 to 2003) were systematically searched for evidence relevant to this special report.

Evidence was selected and reviewed by members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This special report has been reviewed and approved by the Gynecology Cancer Disease Site Group, which is comprised of gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, patient representatives, and methodologists.

Key Evidence

- Eleven randomized controlled trials and one meta-analysis (of five observational studies) were identified that examined the role of complementary or alternative medicine therapies in patients with gynecological cancers. There were no systematic reviews identified describing complementary or alternative medicine therapies specifically for women with gynecological cancers.
- Seven randomized controlled trials compared vitamin A derivatives to placebo in women with precursor cervical cancer or cervical cancer. The evidence suggests that high dosages of vitamin A do not increase regression rates in these women and that there is high toxicity associated with vitamin A.
- One randomized controlled trial compared folic acid to a placebo in women with precursor cervical cancer. There were no differences in regression rates between the two groups.
- One randomized controlled trial and one meta-analysis (of five observational studies) compared vitamin A derivatives to a placebo in women at high risk for developing ovarian cancer. The limited evidence suggests a possible benefit of high-dose vitamin A; however, both studies contain serious design flaws.
- Two randomized controlled trials compared techniques to manage the adverse effects of chemotherapy in women with ovarian cancer. One randomized controlled trial examined relaxation therapy compared to no relaxation therapy and detected that relaxation therapy decreases the adverse effects of chemotherapy compared to no relaxation therapy. The other randomized controlled trial examined electrical stimulation to decrease the adverse effects of chemotherapy compared to no treatment. Women receiving the electrical stimulation reported that they were generally content with its effects, despite a lack of strong evidence supporting the theory that electrical stimulation was truly effective in decreasing nausea.
- One systematic review was identified that reported the safety of various complementary or alternative medicine therapies for patients with various cancer diagnoses. The systematic review advised practitioners to accept and monitor the use of some complementary or alternative medicine therapies including acupuncture, exercise, mind-body therapies, and massage. The systematic review advised practitioners to discourage the use of high

dosages of vitamin A and vitamin C, due to evidence indicating that the vitamins offer no benefit and the high toxicity of the vitamins (particularly vitamin A).

- One meta-analytical review was identified that examined relaxation training in cancer patients. The authors of the review established that patients receiving relaxation training experience significantly less adverse effects associated with cancer treatments than patients who do not receive relaxation training.

For further information about this Special Report, please Dr. Michael Fung Kee Fung, Chair, Gynecology Cancer Disease Site Group, Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario; Telephone: 613-737-8560, FAX: 613-737-8828.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit http://www.cancercare.on.ca/ for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Special Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1]

, The PEBC also develops Special Reports to meet identified needs. Special Reports address clinical issues outside the traditional portfolios covered by the Disease Site Groups. The Reports undergo a modified external review and are approved by the Practice Guidelines Coordinating Committee.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO website at:
http://www.cancercare.on.ca
For more information, contact our office at:
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FULL REPORT

I. QUESTION

1. What complementary or alternative medicine (CAM) therapies are available to women with gynecological cancers?
2. How safe are the CAM therapies available to women with gynecological cancers?

II. CHOICE OF TOPIC AND RATIONALE

Complementary and alternative medicine (CAM) encompasses a wide range of healing philosophies and therapies, including herbal preparations, reflexology, acupuncture, and traditional Chinese medicine. Complementary therapy generally refers to therapies used in addition to conventional therapy, and alternative therapy refers to therapies used instead of conventional therapy. High-quality evidence supporting or refuting the use of CAM therapies is limited. Despite the lack of evidence, there are over 17,000 health-related Web sites, and, unfortunately, none of the data in those Web sites are regulated (1). Nonetheless, the use of CAM therapies seems to be increasing in popularity. Von Gruenigen et al (2) reported survey results that found that 66% of women diagnosed with a gynecological malignancy were using some sort of CAM therapy. In 1999, a survey of the complementary practitioners in Canada found that over 30% of their patients were women over 40 years of age with cancer (3).

An estimated 1,840 women in Ontario were diagnosed with gynecological cancer (endometrium, ovary, cervix) in 2003 (4). Conventional therapies for gynecological cancers include surgery, chemotherapy, radiotherapy and hormonal therapy. Those treatments have been shown to be effective, but the outcome for the individual patient is unknown and, generally, those treatments involve adverse effects. Some women choose CAM therapies to treat their cancer, to manage the adverse effects of conventional treatment, or to gain a sense of control over their disease (1).

As with any treatment, practitioners are concerned about the potential benefits and adverse effects of CAM therapies. The purpose of this special report is to provide information on CAM therapies, primarily regarding safety and efficacy, to conventional practitioners treating women with gynecological cancers. The aim is to increase awareness about the growing field of CAM therapies.

III. BACKGROUND

In a recent study, Swisher et al (5) surveyed 113 women with gynecologic cancers and found that half (49.6%) of the women had used CAM therapies since being diagnosed with cancer and that fewer than 25% of CAM users had received information regarding CAM from a physician, nurse, or practitioner of CAM therapies. Women used CAM therapies in hopes of achieving a wide range of potential benefits, including improved wellbeing and anti-cancer effects. The most common actual benefit these women perceived was an improvement in psychosocial wellbeing, including increased hope or optimism.

Swisher et al (5) reported that women who earned more than $30,000 per annum and women who had used CAM therapies in the past were significantly more likely to use CAM therapies than were women who earned less than $30,000 per annum and women who had not used CAM therapies in the past ($p<0.01$).

The specific types of CAM therapy used by the women surveyed in Swisher et al's (5) survey were divided into the following categories: ingestibles, psychological/spiritual therapies (including faith healing, healing touch, hypnosis, and mental imagery), and other (including reflexology, acupuncture, electro-magnetic therapy, etc.). As expected, many women used multiple CAM therapies. Of the 56 CAM therapy users, 26 (46%) ingested some type of CAM therapy such as herbal therapies or other plant extracts, high-dose vitamins, medicinal teas (including green teas and Essiac), and shark cartilage. Forty-four women (79% of users) used a

psychological or spiritual therapy. Twelve women (21% of users) used another form of CAM therapy (e.g. reflexology, acupuncture, electromagnetic therapy).

When the women surveyed were asked why they were using the CAM therapy, the most common reasons reported were “to do everything possible to fight the cancer” and “to increase the body’s ability to fight cancer”. Table 1 describes all the reasons women listed for using CAM therapies in the survey by Swisher et al (5).

Table 1. Reasons for using CAM therapy (5).

Reason given for using CAM therapy	# of women who listed reason for using CAM therapy (%)	# of women who perceived benefit from CAM therapy (%)
Directly fight the cancer with CAM therapy	9 (36)	1 (7)
Increase the body's ability to fight cancer	16 (64)	2 (22)
Improve physical wellbeing	11 (44)	10 (34)
Improve emotional wellbeing, provide hope, increase optimism, etc.	15 (60)	18 (67)
Counteract ill effects from the cancer or medical treatment	6 (24)	6 (22)
"Might help, can't hurt"	8 (32)	NR
To do everything possible to fight the cancer	16 (64)	NR

Note: CAM, complementary or alternative medicine; NR, not reported.
Table is a modified version of a table in: Swisher EM, Cohn DE, Goff BA, Parham J, Herzog TJ, Rader JS, et al. Use of complementary and alternative medicine among women with gynecologic cancers. *Gynecol Oncol* 2002;84:363-7.

IV. METHODS

Special Report Development

This special report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by members of the PGI’s Gynecology Cancer Disease Site Group (DSG) and methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict of interest information. This special report is intended as information for individuals and groups regarding the benefits and adverse effects associated with CAM therapies for women with gynecological cancers.

The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1985 to April 2004), CANCERLIT (1985 to October 2002), AMED (Allied and Complementary Medicine) (1985 to March 2004) and Cochrane Library (2004, issue 1) databases were searched. “Neoplasms” (Medical subject heading (MeSH)) and types of gynecological malignancies (i.e., endometrial, ovarian, cervical) were combined with forms of CAM medicine. These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials and controlled clinical trials. The full search strategy is listed in Appendix 1. In addition, the conference proceedings of the American Society of Clinical Oncology (1997 to 2003) were searched for reports of new trials. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Outcomes of interest include survival, quality of life, palliative effects, response rate and toxicity. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were searched for existing evidence-based practice guidelines.

Inclusion Criteria

Articles were selected for inclusion in this special report if they were:

1. Systematic reviews or meta-analyses examining CAM therapy for women diagnosed with a gynecological cancer, or if there were no systematic reviews or meta-analyses identified for women with gynecological cancers, then systematic reviews or meta-analyses examining CAM therapies for cancer patients or;
2. Randomized controlled trials (RCTs) comparing a CAM therapy with no therapy or with the standard therapy in women diagnosed with a gynecological cancer, and;
3. If the study reported data on at least one of the outcomes of interest: survival, quality of life, palliative effects, response rate, or toxicity.

Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.

Synthesizing the Evidence

The trials of the various CAM therapies were too heterogeneous to pool because all the therapies and patient populations are unique. There were not enough trials on one particular CAM therapy to pool the results. The Gynecology Cancer DSG considered pooling the outcomes of the use of vitamin A derivatives in women with cervical cancer but decided not to pool the studies due to the variation in stages of cervical cancer, vitamin A derivatives used, methods of administration of the supplement (oral, topical, injection), and outcomes reported.

V. RESULTS

Literature Search Results

There were no systematic reviews identified that specifically discussed the role of CAM therapies in women with gynecological cancers. There were two reviews of CAM therapies that included patients with a variety of cancer diagnoses (6,7). In addition, a meta-analysis of five observational studies was identified that investigated the relationship between vitamin A derivatives and ovarian cancer (8). Eleven RCTs were identified that examined the use of CAM therapies in women with gynecologic malignancies, eight RCTs for cervical cancer (9-16) and three RCTs for ovarian cancer (17-19).

Preinvasive and Invasive Cervical Cancer

Seven RCTs were identified that compared various derivatives of vitamin A (retinoic acid, beta-carotene, etc.) with no vitamin A in women with cervical cancer or precursor cervical cancer lesions (9-15). Of the seven RCTs, five examined the possible chemopreventive effects of vitamin A (9-12,15) and two RCTs incorporated the use of vitamin A with chemotherapy for women with squamous cervical carcinoma (14) or recurrent cervical cancer (13). Another RCT was identified that examined the role of folic acid in chemoprevention by comparing women who took folic acid supplements with women who did not (16). Table 2 describes the RCTs comparing vitamin A derivative therapies for cervical cancer.

Table 2. RCTs comparing vitamin A derivative CAM therapies for cervical cancer.

Study	Patient population	Comparison	Estimation of regression rate	Actual regression rate	Drop out rate
Alvarez, 2003 (9)	114 women with CIN 2/3	High-dose aliretinoin (50mg) (12 weeks)	35%	36%	2%
		Low-dose aliretinoin (25mg) (12 weeks)	35%	32%	
		Placebo (12 weeks)	5%	32% (p=NS)	
Follen, 2001 (10)	39 women with CIN 2/3	4-HPR (200mg) (6 months)	40% CIN2 72% CIN3	25%	8%
		Placebo (6 months)	10% CIN2 30% CIN3	44% (p=NS)	
Keefe, 2001 (11)	103 women with CIN 2/3 (25 lost to follow-up)	Oral beta-carotene (30mg) (2 years)	30-50%	25%	24%
		Placebo (2 years)	10-28%	38% (p=NS)	
Palan, 1998 (12)	69 women with CIN 1/2	Oral beta-carotene (30mg) (9 months)	NR	23%	29%
		Placebo (9 months)	NR	47% (p=0.04)	
Weiss, 1998 (13) (Phase II RCT)	63 recurrent cervical cancer	Oral 13cRA (1mg/kg/day) + IFN-α	10-30% greater than control	8%	8%
		Oral ATRA ($150mg/m^2$/day) + IFN-α	--	5%	
Kim, 1996 (14)	40 cervical cancer	Neoadjuvant chemotherapy + 13cRA	NR	35%	0%
		Neoadjuvant chemotherapy	NR	30% (p>0.05)	
Meyskens, 1994 (15)	301 women with CIN 2/3	Cervical cap with 1.0 mL of 0.372% beta-trans-retinoic acid daily for 4 days, then 2 days at 3 and 6 months	NR	43% CIN2 25% CIN3	23%
		Placebo	NR	27% CIN2 (p=0.04) 31% CIN3 (p=NS)	

Note: 4-HPR, 4-hydroxyphenylretinamide; 13cRA; 13-cis-retinoic acid; ATRA, all-trans-retinoic acid; CAM, complementary and alternative medicine; CIN, cervical intraepithelial neoplasia; IFN, interferon-α ; NS, not significant; RCT, randomized controlled trial

A consistent concern in all those studies is the estimation of the regression rate. Rates of 32% to 57% for the spontaneous regression of cervical intraepithelial neoplasia (CIN) have been reported in natural history studies, depending on the grade of disease (a lower grade suggests a higher rate of spontaneous regression) (20). Four RCTs provided estimations of the regression rate; all four RCTs predicted a less than 30% regression rate in the control arm, when the natural history of the disease suggests that spontaneous regression will be greater than 30% (9-11,13). Another concern about the RCTs is their dropout rates. The duration of the studies varied from four to 24 months. The 24-month study by Keefe et al (11) screened 982 patients and enrolled 124. One hundred three patients were included in the analysis, but 25 were lost to follow-up (24% dropout rate). Women included in the two RCTs that compared chemotherapy with or without vitamin A derivatives (13,14) had lower dropout rates, possibly because their treatment was for their disease rather than to prevent cervical cancer.

Women included in the chemoprevention trials were diagnosed with precursor cervical cancer or CIN. One RCT detected a greater regression rate among women taking the placebo compared with those taking the vitamin A derivative (p=0.04) (12), and one RCT detected a

greater regression rate among women diagnosed with CIN2 who were taking the vitamin A derivative as opposed to the placebo (p=0.04). However, the difference in regression rates was not observed in women diagnosed with CIN3 (15). The other three RCTs did not detect a difference in regression rates between women taking vitamin A derivatives and women taking the placebo (9-11). Neither of the studies comparing chemotherapy with or without vitamin A derivatives detected a significant difference in the regression rates between the treatment and placebo groups (13,14).

As mentioned previously, one additional RCT comparing a CAM therapy for women with cervical cancer was identified (16). Childers et al (16) randomized 331 women with CIN to receive either daily oral folic acid (5mg/day) or a placebo for six months. Women underwent colposcopy and Papanicolaou smears every three months. Childers et al (16) did not detect a difference between treatment groups after six months.

Endometrial Cancer

No RCTs were found that compared various CAM therapies for endometrial cancer.

Ovarian Cancer

One RCT (17) and a meta-analysis (8) (of five observational studies) were identified that investigated the relationship between vitamin A derivatives and ovarian cancer. Two additional RCTs were identified that examined CAM therapies for women with ovarian cancer to manage the adverse effects of chemotherapy (18,19).

Prevention of ovarian cancer

De Palo et al (17) randomized 2,867 women who had been previously treated for breast cancer to receive either fenretinide (200 mg per os daily, for 5 years) or no treatment (control group). De Palo et al detected that during the intervention six women in the control group were diagnosed with ovarian cancer, compared to no women in the fenretinide group (p=0.03). After the intervention, four women in the control group and six women in the fenretinide group were diagnosed with ovarian cancer (p=0.76). Overall, 10 women in the control group (0.7%) and six women in the fenretinide group (0.42%) developed ovarian cancer; however, De Palo et al did not report if this difference in incidence was significant. De Palo et al (17) did not report any toxicity data for their RCT.

A meta-analysis of five observational studies on beta-carotene intake and ovarian cancer risk included 3,782 healthy women. Huncharek et al (8) reported that women who had high dietary intakes of beta-carotene had a 16% decrease in ovarian cancer compared to women with low dietary intakes of beta-carotene. However, it is important to recognize that this difference was calculated from observational studies, not randomized trials.

Management of ovarian cancer symptoms and adverse effects of treatment

Lekander et al's RCT (19) compared the immune effects of relaxation therapy to no treatment in 22 women receiving chemotherapy for ovarian cancer. They found that the 12 patients who received two months of relaxation therapy training had significantly higher levels of lymphocytes than did the control group (p<0.01). The patients who received relaxation therapy also displayed a tendency towards higher white blood cell counts (p<0.09) and higher levels of monocytes (p<0.09) than did the control group. That RCT did not include a complete assessment of white blood cells at baseline; thus, the differences observed between the groups could have existed prior to the relaxation intervention. Also, this was a very small study with a small sample size.

Another RCT compared the effects of transcutaneous electrical nerve stimulation (TENS) to no treatment in 32 women with gynecologic cancers (56% of patients diagnosed with ovarian cancer) (18). Nausea was measured as an outcome measure. There was no

significant difference between the treatment and the control groups with respect to vomiting. Fifty-six percent of the patients in the treatment group reported minimal or no nausea compared with 62% in the control group (no p-value reported). Despite this small difference, when the patients were asked about their satisfaction with the TENS (Relief Band), they said they were generally satisfied, and 75% said they would recommend it to other patients undergoing chemotherapy (18).

How safe are the CAM therapies available to women with gynecological cancers?

The literature search identified four different CAM therapies evaluated in women with gynecological cancers. Table 3 outlines therapies and their safety. However, there is limited information on the actual safety of CAM therapies.

Table 3. The CAM therapies evaluated in this special report for women with gynecological cancers.

CAM therapy	Intent of therapy	Level of evidence	Safety
Folic acid	To affect disease progression	1 RCT	• Not reported
Relaxation therapy	Palliation of symptoms	1 RCT	• Not reported
TENS	Palliation of symptoms	1 RCT	• Possible skin irritation
Vitamin A derivatives	To affect disease progression	7 RCTs 1 meta-analysis	• Increased vulva burning, itching and irritation compared to control group (15) • More skin yellowing in treatment group than control group (11) • No significant differences in toxicity between groups (9)

Note: CAM, complementary or alternative medicine; RCT, randomized controlled trial; TENS, transcutaneous electrical nerve stimulation.

Systematic Reviews of CAM Therapies in Patients With Various Cancer Diagnoses

There were two reviews of CAM therapies that included patients with a variety of cancer diagnoses (6,7). In 2002, Weiger et al (7) published a systematic review of CAM therapies with the intention of advising practitioners on how to inform their patients about the use of CAM therapies. Weiger et al (7) were primarily interested in the safety of the CAM therapies. They also provided some results on the effectiveness of the various therapies. Table 4 provides an overview of the CAM therapies investigated and the type of evidence available. They noted that patients have the right to choose whether or not they use CAM therapies, and the role of the practitioner is to be aware and monitor the therapies. Weiger et al strongly advised against the use of vitamins A and C. As mentioned previously in this report, vitamin A derivatives have been studied in women with early signs of cervical cancer. The results of the previously mentioned studies are consistent with the findings of Weiger et al: high dosages of vitamin A are toxic and do not seem to decrease the incidence of invasive cervical cancer. No studies identified observing the affects of vitamin C in women with gynecological cancers. There were, however, two RCTs identified that compared treatment alone to treatment with high-dose vitamin C in patients with advanced cancer. Neither trial detected a survival benefit in the patients treated with vitamin C. In addition, high dosages of vitamin C have anticoagulation effects. That is, high dosages of vitamin C inhibit platelet aggregation. Thus, patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery should avoid high dosages of vitamin to avoid the risk of bleeding.

Luebbert et al (6) published a meta-analytical review of relaxation training in the management of non-surgical treatment symptoms in patients with cancer. They included 15

studies in their meta-analysis (N=742). Nine studies specifically addressed the effects of chemotherapy, three specifically addressed the effects of radiation therapy, two examined the effects of bone marrow transplantation, and the final study addressed the effects of hyperthermia. They reported that patients who received relaxation training suffered significantly less pain and nausea than patients who did not receive relaxation training ($p<0.05$). Luebbert et al acknowledge some limitations of their meta-analysis, including external validity. The majority of the patients included in the meta-analysis were women over 55 years. The most common cancers of the patients in the meta-analysis were breast, hematological, lymphoma, and lung. The methods of relaxation training varied across studies as well. However, despite the variation in relaxation instruction, the training did have significant beneficial effects on the patients.

Table 4. CAM therapies investigated in Weiger et al's (7) systematic review.

CAM therapy	Intent of therapy	Level of evidence	Safety	Contraindications	Advice suggested by Weiger (7)
Acupuncture for chemotherapy effects	Palliation of symptoms	High: RCTs	Evidence to suggest minor adverse effects	• avoid in patients receiving anticoagulant therapy	Accept (consider recommending) and monitor
Acupuncture for chronic pain	Palliation of symptoms	Low: opinions, descriptive studies	Evidence to suggest minor adverse effects	• avoid in patients receiving anticoagulant therapy	Accept and monitor
Exercise to improve physical and psychological function	Palliation of symptoms	High: RCTs	Probably no adverse effects; however, there are not enough clinical cases to make conclusion	• avoid in patients who are prone to fractures, febrile, dehydrated, or who have abnormal electrolyte levels	Accept (consider recommending) and monitor
Macrobiotic diet	To affect disease progression	Low: opinions, descriptive studies	Probably no adverse effects; however, there are not enough clinical cases to make conclusion	• avoid in women with endometrial cancer • avoid in patients with poor nutritional status	Accept and monitor
Massage for anxiety	Palliation of symptoms	High: RCTs	Evidence to suggest minor adverse effects	• avoid in patients receiving anticoagulant therapy	Accept (consider recommending) and monitor
Massage for pain	Palliation of symptoms	High: RCTs	Evidence to suggest minor adverse effects	• avoid in patients receiving anticoagulant therapy	Accept and monitor
Mind-body therapies	To affect disease progression	High: RCTs	Probably no adverse effects; however, there are not enough clinical cases to make conclusion	• none identified	Accept and monitor
Shark cartilage	To affect disease progression	Low: opinions, descriptive studies	Evidence to suggest minor adverse effects	• avoid in patients with hypercalcemia • avoid in patients who may be pregnant • avoid in patients with vascular insufficiency	Accept and monitor
Vitamin A	To affect disease progression	High: RCTs	Evidence of major (life threatening) adverse effects	• avoid concurrent use with RT or CT • avoid in patients who may be pregnant	Discourage and monitor
Vitamin C	To affect disease progression	High: RCTs	Probably no adverse effects; however, there are not enough clinical cases to make conclusion	• avoid concurrent use with RT or CT • avoid in patients receiving anticoagulant therapy	Discourage and monitor

Note: CAM, complementary and alternative medicine; CT, chemotherapy; RCT, randomized controlled trial; RT, radiotherapy;
Table is a modified version of a table in Weiger WA, Smith M, Boon H, Richardson MA, Kaptchuk TJ, Eisenberg DM. Advising patients who seek CAM therapies for cancer. Ann Intern Med. 2002;137:889-E-913.

VI. INTERPRETIVE SUMMARY

Given the high prevalence of CAM usage in the patient population, practitioners treating women with gynecologic cancers should ask these women about CAM usage as early as the initiation of cancer care. Since previous CAM usage strongly predicts for subsequent use of CAM therapies, this issue can be discussed even at the initial visit. A benefit to discussing CAM therapies with patients is the possible identification of important quality-of-life issues (such as anxiety, depression, nausea, neuropathy, and fatigue) that are not being addressed to the patient's satisfaction, enabling a discussion about conventional alternatives.

It is important to educate patients about the potential dangers of CAM usage, especially as there is limited evidence regarding the harms and benefits of CAM therapies. CAM therapies need to be assessed concerning adverse effects, quality control, and contamination. The Memorial Sloan-Kettering Cancer Centre has a comprehensive list of herbal therapies listed on their Web site (http://www.mskcc.org/mskcc/html/11570.cfm) and includes information for health care professionals regarding the purported uses of herbal therapy, adverse reactions, and drug interactions.

Unfortunately, there is still insufficient evidence available to strongly support or refute the use of most CAM therapies in women with gynecological cancers. The Gynecology Cancer DSG formulated some opinions based on the limited evidence available; however, until there is more evidence, the Gynecology Cancer DSG decided not to make recommendations. More research needs to be conducted to clarify the role that CAM therapy can play in the prevention and treatment of gynecological cancers. In 2001, Cancer Care Ontario developed a position statement regarding the use of CAM therapies and posted it on their Web site http://www.cancercare.on.ca/access_livingWithCancer.htm (accessed July 6, 2004). The statement acknowledges the paucity of high-quality evidence but recognizes that some patients are interested in pursuing non-conventional treatments. The position statement encourages patients and practitioners to openly discuss unconventional treatments.

VII. ONGOING TRIALS

Physician Data Query (PDQ) clinical trials database on the Internet was searched for ongoing trials (http://www.cancer.gov/clinical_trials/). There were no ongoing trials identified through the PDQ, but, there was one trial identified through Internet search engine (www.google.ca) search. The University of Kansas Medical Center's Kansas Cancer Institute is conducting a randomized trial of the antioxidant effects in the treatment of ovarian cancer (stage III-IV) (http://www2.kumc.edu/kci/protocols/AntioxidantFlyer.doc, accessed May 5, 2004).

VIII. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Draft Opinions

Based on the evidence reviewed, the Gynecology Cancer DSG drafted the following opinions:

Target Population

This special report applies to women seeking or using complementary or alternative medicine therapies to prevent or treat a gynecological cancer.

Draft Opinions of the Gynecology Cancer DSG

The lack of sufficient high-quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer DSG offers the following opinions based on the evidence reviewed:

- From the evidence available from RCTs investigating CAM therapies for the prevention or treatment of malignancies of all types, the Gynecology Cancer DSG feels that:

- Women with gynecological malignancies should be discouraged from using vitamin A and vitamin C for the purpose of delaying progression of the malignancy. Not only are these vitamins highly toxic, but also there is no evidence to support that the vitamins are beneficial.
- Women with gynecological malignancies may be encouraged to engage in physical activity (as possible) or relaxation therapy to improve physical and psychological function.
- The Gynecology Cancer DSG is unable to support or refute the use of any other CAM therapy based on the limited evidence.

- Practitioners should ask their patients if they are using or considering CAM therapies.

Practitioner Feedback

A draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the 'Modifications' section below.

Methods

The Gynecology Cancer DSG wanted feedback from alternative and complementary medicine practitioners in the province, 10 letters were sent to alternative and complementary practitioners in Ontario in September 2003 asking if they would be interested in participating in the PGI's practitioner feedback process. Four of the practitioners responded, indicating that they would be interesting in providing feedback on this special report.

Practitioner feedback was obtained through a mailed survey of 12 practitioners in Ontario (five medical oncologists, three gynecologists, and four alternative and complementary medicine practitioners). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on November 1, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The alternative and complementary practitioners who had not responded by January 1, 2004 were sent a third package. The Gynecology Cancer DSG reviewed the results of the survey.

Results

Six responses were received out of the 12 surveys sent (50% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Two of the four alternative and complementary medicine practitioners returned surveys; however, they both indicated that the special report was not relevant to their clinical practice, and thus did not complete the survey. Of the practitioners who responded, three indicated that the report was relevant to their clinical practice and completed the survey. Results of the practitioner feedback survey are summarized in Table 5.

Table 5. Results of the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing an evidence summary, as stated in the "Choice of Topic" section of the report, is clear.	3 (100%)	--	--
There is a need for an evidence summary on this topic.	2 (67%)	1 (33%)	--
The literature search is relevant and complete in this evidence summary.	3 (100%)	--	--
I agree with the methodology used to summarize the evidence.	3 (100%)	--	--
I agree with the overall interpretation of the evidence in the evidence summary.	3 (100%)	--	--
The "Opinions of the Gynecology Disease Site Group" section of this evidence summary is useful.	3 (100%)	--	--
An evidence summary of this type will be useful for clinical decision making.	2 (67%)	1 (33%)	--
At present, there is insufficient evidence to develop a practice guideline on this topic.	2 (100%)	--	--
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	3 (100%)	--	--

Summary of Written Comments

Two respondents (66%) provided written comments. The main points contained in the written comments were:

1. More relevant would be therapies such as Essiac or 714-X.
2. The special report is good; however, should the report be limited to RCTs?

Modifications/Actions

1. The literature search strategy included 186 different alternative or complementary therapies; neither Essiac nor 714-X were included in the original list. Those two therapies were included in a revised literature strategy. No additional RCTs were identified that specifically examined women seeking or using complementary or alternative medicine therapies to prevent or treat a gynecological cancer
2. The Gynecology Cancer DSG chose to limit the literature search to RCTs because the quality and methodologic rigor of many studies investigating alternative and complementary therapies is weak and by selecting only RCTs the Gynecology Cancer DSG felt they were able to control for the poor quality of many of the studies.

Practice Guidelines Coordinating Committee Approval Process (PGCC)

The special report was circulated to members of the PGCC for review and approval. Eight of 14 members of the PGCC returned ballots. Four PGCC members approved the special report as written, and one member approved the report with minor modifications required. One member approved the report with suggestions for consideration by the Gynecology DSG. Two members approved the report conditional on the DSG addressing their comments. One PGCC member noted that the 'Opinion' statement regarding vitamin A and vitamin C was problematic because it did not indicate that it was the high dosages of the vitamins that were toxic. Two PGCC members also noted that the evidence regarding the statement about vitamin C was not specific to gynecological cancers. Another PGCC member thought that the Gynecology Cancer DSG should make reference to CCO's position statement regarding the use of CAM therapies.

Modifications/Actions

The 'Opinions' section was modified to separate the 'Opinion' statements for vitamin A and vitamin C. The statement regarding vitamin C clearly indicates that there is no evidence

specifically investigating high dose vitamin C in women with gynecological cancers. Also, the statements were revised to indicate that it is high dosages of the vitamins that are toxic. The Gynecology Cancer DSG included a section in the Interpretive Summary regarding CCO's position statement on CAM therapies.

IX. OPINIONS OF THE GYNECOLOGICAL CANCER DISEASE SITE GROUP

The lack of sufficient high-quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer Disease Site Group offers the following opinions based on the evidence reviewed:

- From the evidence available from randomized controlled trials investigating complementary or alternative medicine therapies for the prevention or treatment of malignancies of all types, the Gynecology Cancer Disease Site Group feels that:
  - Women with gynecological malignancies should be discouraged from using high dosages of vitamin A for the purpose of delaying progression of the malignancy. Not only are high dosages of vitamin A highly toxic but also there is no evidence to support that high dosages of vitamin A are beneficial.
  - Women with gynecological malignancies may be encouraged to engage in physical activity (if possible) or relaxation therapy to improve physical and psychological function.
  - There is some evidence refuting that high dosages of vitamin C are beneficial, however, the evidence is not specific to women with gynecological cancers. High doses of vitamin C have anticoagulant effects, which could potentially increase the risk of bleeding in patients who are undergoing surgery or are thrombocytopenic.
  - The Gynecology Cancer Disease Site Group is unable to support or refute the use of any other complementary or alternative medicine therapy based on the limited evidence.
- Practitioners and patients are encouraged to openly discuss and disclose the use of complementary or alternative medicine therapies. Disclosing the use of complementary or alternative medicine therapies will allow practitioners provide assistance and guidance to the extent possible with respect to any potential harms or benefits known to be associated with the use of the therapies.

X. JOURNAL REFERENCE

This special report is a "Web-only" document and will not be submitted to a peer-reviewed journal.

XI. ACKNOWLEDGMENTS

The Gynecology Cancer Disease Site Group would like to thank Mrs. Carmen Briere, Ms. Dianne Dal Bello, Dr. Michael Fung Kee Fung, and Ms. Alexandra Chambers for taking the lead in drafting and revising this special report.

For a complete list of Gynecology Cancer Disease Site Group members, please visit the CCO website at http://www.cancercare.on.ca/.

REFERENCES

1. Gertz MA, Bauer BA. Caring (really) for patients who use alternative therapies for cancer. J Clin Oncol. 2001;19:4346-9.
2. Von Gruenigen VE, Hopkins MP. Alternative medicine in gynecologic oncology: A case report. Gynecol Oncol. 2000;77:190-2.
3. Gray RE, Ftich M, Saunders PR, Wilkinson A, Ross CP, Franssen E, et al. Complementary health practitioners' attitudes, practices and knowledge related to women's cancers. Cancer Prev Control. 1999;3:77-82.
4. National Cancer Institute of Canada. Canadian cancer statistics 2003. Toronto, Canada; 2003.
5. Swisher EM, Cohn DE, Goff BA, Parham J, Herzog TJ, Rader JS, et al. Use of complementary and alternative medicine among women with gynecologic cancers. Gynecol Oncol. 2002;84:363-7.
6. Luebbert K, Dahme B, Hasenbring M. The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. Psychooncol. 2001;10:490-502.
7. Weiger WA, Smith M, Boon H, Richardson MA, Kaptchuk TJ, Eisenberg DM. Advising patients who seek complementary and alternative medical therapies for cancer. Annal Intern Med. 2002;137:889-913.
8. Huncharek M, Klassen H, Kupelnick B. Dietary beta-carotene intake and the risk of epithelial ovarian cancer: a meta-analysis of 3,782 subjects from five observational studies. In Vivo. 2001;15:339-43.
9. Alvarez RD, Conner MG, Weiss H, Klug PM, Niwas S, Manne U, et al. The efficacy of 9-cis-retinoic acid (Aliretinoin) as a chemopreventive agent for cervical dysplasia: results of a randomized double-bind clinical trial. Cancer Epidemiol Biomarker Prev. 2003;12:114-9.
10. Follen M, Atkinson EN, Schottenfeld D, Malpica A, West L, Lippman S, et al. A randomized clinical trial of 4-hydroxyphenylretinamide for high-grade squamous intraepithelial lesions of the cervix. Clin Cancer Res. 2001;7:3356-65.
11. Keefe KA, Schell MJ, Brewer C, McHale M, Brewster W, Chapman JA, et al. A randomized, double blind, phase III trial using oral beta-carotene supplementation for women with high-grade cervical intraepithelial neoplasia. Cancer Epidemiol Biomarker Prev. 2001;10:1029-35.
12. Palan PR, Chang CJ, Mikhail MS, Ho GYF, Basu J, Romney SL. Plasma concentrations of micronutrients during a nine-month clinical trial of beta-carotene in women with precursor cervical cancer lesions. Nutr Cancer. 1998;30:46-52.
13. Weiss GR, Liu PY, Alberts DS, Peng YM, Fisher E, Xu MJ, et al. 13-cis-retinoic acid or all-trans-retinoic acid plus interferon-alpha in recurrent cervical cancer: a Southwest Oncology Group phase II randomized trial. Gynecol Oncol. 1998;71:386-90.
14. Kim JW, Kim YT, Choi SM, Kim DK, Song CH. Effect of 13-cis-retinoic acid with neoadjuvant chemotherapy in patients with squamous cervical carcinoma. Am J Clin Oncol. 1996;19:442-4.
15. Meyskens FL, Surwit E, Moon TE, Childers JM, Davis JR, Dorr RT, et al. Enhancement of regression of cervical intraepithelial neoplasia II (moderate dysplasia) with topically applied all-trans-retinoic acid: A randomized trial. J Natl Cancer Inst. 1994;86:539-43.
16. Childers JM, Chu J, Voigt LF, Feigl P, Tamimi HK, Franklin EW, et al. Chemoprevention of cervical cancer with folic acid: a phase III Southwest Oncology Group Intergroup Study. Cancer Epidemiol Biomarkers Prev. 1995;4:155-9.
17. De Palo G, Mariani L, Camerini T, Marubini E, Formelli F, Pasini B, et al. Effect of fenretinide on ovarian carcinoma occurrence. Gynecol Oncol. 2002;86:24-7.

18. Pearl ML, Fischer M, McCauley DL, Valea FA, Chalas E. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induces nausea and vomiting in gynecologic oncology patients. Cancer Nurs. 1999;22:307-11.
19. Lekander M, Furst CJ, Rotstein S, Husti TJ, Fredrikson M. Immune effects of relaxation during chemotherapy for ovarian cancer. Psychother Psychosom. 1997;66:185-91.
20. Follen M, Meyskens FL, Atkinson EN, Schottenfeld D. Why most randomized phase II cervical cancer chemoprevention trials are uninformative: lessons for the future. J Natl Cancer Inst. 2001;93:1293-6.

Appendix 1. Literature search strategy.

1 shark cartilage.tw. (86)
2 AE-941.tw. (12)
3 allantoin.tw. (494)
4 comfrey.tw. (36)
5 aloe.tw. (379)
6 herbal remed:.tw. (523)
7 greek cancer cure.tw. (2)
8 amygdalin.tw. (150)
9 laetrile.tw. (336)
10 antineoplastons.tw. (25)
11 antioxidant vitamin:.tw. (1146)
12 vitamin:.tw. (70825)
13 arctium lappa.tw. (26)
14 essiac.tw. (9)
15 aristolochia.tw. (134)
16 ascorbic acid.tw. (11852)
17 vitamin c.tw. (6493)
18 astra 8.tw. (35)
19 mushroom therap:.tw. (0)
20 astragalus.tw. (436)
21 barley.tw. (4575)
22 benefin.tw. (10)
23 beta-carotene.tw. (4817)
24 vitamin a.tw. (50529)
25 bioflavanoids.tw. (0)
26 pycnogenol.tw. (54)
27 bio-oxidative therapy.tw. (1)
28 oxygen therap:.tw. (3778)
29 blackwort.tw. (1)
30 buckthorn bark.tw. (1)
31 hoxsey's herbal tonic.tw. (0)
32 burdock.tw. (38)
33 immunoaugmentative therapy.tw. (13)
34 IAT.tw. (285)
35 calcitriol.tw. (1892)
36 vitamin d.tw. (14701)
37 calico flower.tw. (0)
38 canaid.tw. (0)
39 cancell.tw. (4)
40 carotenes.tw. (303)
41 cartilade.tw. (0)
42 cartilate.tw. (3)
43 cassava.tw. (571)
44 chacon cancer cure.tw. (0)
45 chamomile tea.tw. (10)
46 chaparral tea.tw. (1)
47 cholecalciferol.tw. (754)
48 chondriana.tw. (0)
49 clover juice.tw. (0)
50 red clover.tw. (222)
51 coenzyme Q.tw. (701)
52 coumarins.tw. (652)
53 lentinan.tw. (305)
54 mushroom therap:.tw. (0)
55 lentinula edodes.tw. (44)
56 life crystals.tw. (0)
57 livingston therap:.tw. (0)
58 macrobiotic diets.tw. (23)
59 manchurian tea.tw. (0)
60 kombucha.tw. (20)
61 mankind research foundation.tw. (0)
62 megadose vitamin:.tw. (28)
63 vitamin therap:.tw. (256)
64 melilot.tw. (8)
65 dimethyl sulfoxide.tw. (5136)
66 DMSO.tw. (5639)
67 mistletoe.tw. (676)
68 iscador.tw. (93)
69 mo-gu.tw. (0)
70 mushroom:.tw. (3129)
71 714X.tw. (2)
72 NDGA.tw. (841)
73 neovastat.tw. (14)
74 neirum oleander.tw. (0)
75 nerium oleander.tw. (48)
76 niacin.tw. (1526)
77 nicotinic acid.tw. (2583)
78 nitriloside.tw. (3)
79 laetrile.tw. (336)
80 nordihydroguaiaretic acid.tw. (1465)
81 orthomolecular therap:.tw. (6)
82 oxidative therap:.tw. (8)
83 oxygen therap:.tw. (3778)
84 oxidiolog:.tw. (0)
85 hydrogen peroxide.tw. (15327)
86 oxymedicine.tw. (1)
87 ozone.tw. (4580)
88 pyrrolizidine alkaloid:.tw. (663)
89 panax.tw. (728)
90 ginseng.tw. (1294)
91 paraguay tea.tw. (4)
92 pau d'arco.tw. (4)
93 peppermint tea.tw. (2)
94 creosote bush.tw. (17)
95 devil's claw root.tw. (0)
96 dimethyl sulfoxide.tw. (5136)
97 dutchman's pipe.tw. (1)
98 eden foundation.tw. (1)
99 eleuthero.tw. (1)
100 entelev.tw. (1)
101 faith healing.tw. (95)
102 psychic surger:.tw. (8)
103 Fan Ji.tw. (0)
104 fangchi.tw. (15)
105 flor essence.tw. (1)
106 fungo japon.tw. (0)
107 ganoderma.tw. (221)
108 gerson therap:.tw. (2)
109 ginger.tw. (336)
110 glyoxylide.tw. (0)
111 koch treatment.tw. (1)
112 hydrazine sulfate.tw. (145)
113 green tea.tw. (985)
114 grifola frondosa.tw. (62)
115 harpagoside.tw. (27)
116 helixor.tw. (11)
117 hoxsey herbal treatment.tw. (0)
118 hoxsey method.tw. (1)
119 hoxsey.tw. (4)
120 hydarzine sulphate.tw. (0)
121 hydrazine sulphate.tw. (27)
122 hydrazinium.tw. (26)
123 hydra-zonium sulfate.tw. (0)
124 hyperoxygenation therap:.tw. (1)
125 ilex paraguariensis.tw. (33)
126 imagery.tw. (3098)
127 simonton method.tw. (2)
128 indian rhubarb.tw. (1)
129 inkberry.tw. (0)
130 ipe.tw. (139)
131 plenosol.tw. (4)
132 poke.tw. (188)
133 pokeweed.tw. (4313)
134 polybioflavinoid.tw. (0)
135 pycnogenol.tw. (54)
136 prositol.tw. (0)
137 provitamin.tw. (290)
138 pro-vitamin.tw. (43)
139 PSK.tw. (471)
140 psychotherapy method.tw. (25)
141 pyridoxine.tw. (2869)
142 reishi.tw. (3)
143 resperin corporation.tw. (0)
144 retinoids.tw. (5116)
145 rheum palmatum.tw. (53)
146 rumex acetosella.tw. (2)
147 safrole.tw. (209)
148 sassafras tea.tw. (1)
149 sarcarcinase.tw. (0)
150 sheephead sorrel.tw. (0)
151 shiitake.tw. (84)
152 slippery elm.tw. (2)
153 SOD.tw. (8720)
154 superoxide dismutase.tw. (19317)
155 zinc.tw. (37072)
156 steiner.tw. (287)
157 stephania tetranda.tw. (0)
158 sweet woodruff.tw. (0)
159 symphytum officinale.tw. (25)
160 taheebo tea.tw. (1)
161 tannins.tw. (850)
162 thorn apple.tw. (30)
163 tonka beans.tw. (2)
164 trumpet bush.tw. (0)
165 ubiquinone.tw. (2697)
166 ulmus fulva.tw. (0)
167 ipe roxo.tw. (0)
168 iscucin.tw. (1)
169 krebiozen.tw. (7)
170 jimson weed.tw. (29)
171 jin bu huan.tw. (11)
172 knitbone.tw. (0)
173 koch synthetic antitoxin.tw. (0)
174 krestin.tw. (72)
175 kwassan.tw. (0)
176 lapacho.tw. (2)
177 lapacho morado.tw. (0)
178 larrea divericata.tw. (0)

179 larrea tridentata.tw. (20)
180 ulmas rubra.tw. (0)
181 viscumalbum.tw. (0)
182 vitamin B.tw. (2993)
183 vitamin E.tw. (12058)
184 vitamin K.tw. (3974)
185 zen macrobiotics.tw. (1)
186 essiac.tw. (10)
187 714-X.tw. (23)
188 or/1-187 (205379)
189 exp Neoplasms/ (1440932)
190 random:.sh,pt,tw. (345585)
191 controlled:.sh,tw,pt. (234664)
192 clinical trial?.sh,tw,pt. (426058)
193 prospective stud:.sh,tw,pt. (171631)
194 or/190-194 (682201)
195 exp guidelines/ (35634)
196 (practice guidelines or guideline?).tw,pt. (63337)
197 consensus.sh,tw,pt. (39357)
198 or/194-196 (758403)
199 meta-analysis.sh,pt. (11650)
200 (meta-anal: or metaanal: or metanal:).tw. (9542)
201 (systematic: review? or systematic: overview?).tw. (4194)
202 or/199-201 (17490)
203 194 or 198 or 202 (766453)
204 188 and 189 and 203 (2016)
205 endometr:.tw. (34854)
206 uter:.tw. (82877)
207 ovar:.tw. (102875)
208 cerv:.tw. (101044)
209 vulva:.tw. (6420)
210 or/212-216 (284132)
211 204 and 210 (75)

Guideline review outcomes definitions.

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.